CT, MRI, $^{18}$F-FDG-PET, or $^{111}$In-Octreotide? (and what is MIBG?)

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No COI
Let’s start with a case...

- 49 year old female with 1 year history cerebellar ataxia
  - suspected paraneoplastic syndrome secondary to well differentiated neuroendocrine tumor (carcinoid) in stomach
  - 2-2.5 cm
CT and MR
Primary gastric lesion.
No metastases. Incidental focal nodular hyperplasia segment 4b
Before committing to curative surgical resection $^{111}$In-Octreotide is ordered as a complementary study to anatomic imaging.
Change of Management

• Uptake is present not only in known gastric carcinoid but also in segment 4b “FNH”
• MR guided biopsy reveals metastatic NET
  – No other lesions seen
  – Underwent MR thermal ablation
• Subsequent laparoscopic partial gastrectomy
• Unfortunately neurologic symptoms did not regress but patient will undergo close surveillance for her metastatic NET
GEP (Gastroenteropancreatic) NET

• This case demonstrates many issues concerning imaging and approach to GEP NET
GEP NET

• Broad family, arise from enterochromaffin cells, most common
  – Carcinoid
    • most mid-gut
    • serotonin, histamines, tachykinins, 5-HIAA, chromogranin A
  – “Pancreatic” NET
    • may be extra-pancreatic
    • insulinomas, gastrinomas, glucagonomas, VIPomas
    • chromogranin A
Imaging Tools

• Appropriate use of imaging tools dictated by which are available to you and the quality by which they are done.

• Multidisciplinary and multimodality approach essential for optimal evaluation and management.

• Knowledge of pathophysiology can inform imaging.
Carcinoid and Pancreatic NET

- Functional or non-functional
  - **Carcinoid**: syndrome 8% since liver enzymes inactivate
    - Look for liver (or retroperitoneal disease)
    - Most express SSR (related to differentiation)
    - 20% metastases at presentation
      - 50% of those, primary not located at initial imaging
      - Can have sclerotic bone metastases
    - Cardiac disease
Carcinoid and Pancreatic NET

- Functional or non-functional

  - Pancreatic NET majority nonfunctional
    - Functional detected at smaller size
    - Risk of malignancy increases with tumor size
      - 90% nonfunctional malignant at presentation
    - Even nonfunctional can express markers and SSR
    - Of functional, 70% insulinomas; 90% benign
      - 15% glucagonomas
      - 10% gastrinomas and somatostatinomas
        » Higher risk of metastases
Carcinoid and Pancreatic NET

• Most sporadic
  – minority associated with MEN syndrome

• Classification based on differentiation and grade
  – Low, intermediate or high grade (poorly differentiated)

• Subclassified (and staged) by site of origin

• TNM staging
First stop: NCCN Guidelines

Carcinoid Tumors

<table>
<thead>
<tr>
<th>CLINICAL LOCATION</th>
<th>EVALUATION(a,b)</th>
<th>PRIMARY TREATMENT OF NON-METASTATIC DISEASE(c) (If metastatic disease discovered, see CARC-6)</th>
<th>SURVEILLANCE(f,g)</th>
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<tbody>
<tr>
<td>Jejunal/ileal/colon</td>
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<tr>
<td>As appropriate:</td>
<td>Abdominal/pelvic multiphasic CT or MRI</td>
<td>Bowel resection with regional lymphadenectomy</td>
<td>3-12 mo postresection:</td>
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<td></td>
<td>Octreoscan</td>
<td>Consider prophylactic cholecystectomy(d) when appropriate</td>
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<td></td>
<td>Colonoscopy</td>
<td></td>
<td>H&amp;P</td>
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<td></td>
<td>Small-bowel imaging</td>
<td></td>
<td>Consider 5-HIAA</td>
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<td>Consider chromogranin A (category 3)</td>
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<tr>
<td>Duodenal</td>
<td>Duodenal</td>
<td>Endoscopic resection</td>
<td>1 y postresection:</td>
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<tr>
<td>As appropriate:</td>
<td>Abdominal/pelvic multiphasic CT or MRI</td>
<td>Local excision (transduodenal) ± lymph node sampling</td>
<td>6-12 mo thereafter</td>
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<td>Octreoscan</td>
<td>Pancreatoduodenectomy</td>
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<td>EGD/endoscopic ultrasound (EUS)</td>
<td></td>
<td>H&amp;P</td>
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<td>Imaging studies as clinically indicated</td>
</tr>
</tbody>
</table>

See Recurrent or Metastatic Disease (CARC-6)
What to get first?

- The theme in most of the NCCN algorithms is that abdominopelvic multiphasic CT or MR is mandatory.

- As appropriate: $^{111}$In-Octreotide and other techniques (depending on location).
CT or MR?

- CT or MR is the first line imaging that should be done in either potentially resectable or unresectable disease and/or distant disease.
- Each has advantages and disadvantages.
- MR is potentially the better tool but depends on the quality of the modality available to you.
CT or MR

• CT less expensive, less prone to respiratory artifact, but uses ionizing radiation and less sensitive than MR

• MR has exquisite soft tissue contrast, ability to “interrogate” lesions with multi-sequences for optimal characterization and is especially suited for the liver
  – For pancreatic NET: MR generally higher sensitivity 85-94% while CT 57-94.4% depending on protocol
  – Low et al. Radiographics 2011;31:993
CT or MR

- In either case the key to diagnostic CT or MR is multiphasic imaging
  - planning for resection of localized disease including vessel status
  - carcinoid: classic midgut ill-defined enhancing soft tissue mass
    - desmoplastic reaction
    - mesenteric vessels compromised
      - ischemia/thickening adjacent bowel
    - 70% calcifications
CT or MR

• Most carcinoid hepatic metastases and pancreatic NET
  – very rapid arterial phase contrast enhancement which must be detected to achieve high sensitivity
  – MR low on T1, high on T2
What about molecular imaging?

- What are the diagnostic tools in the US?
  - $^{111}$In-Octreotide
  - $^{18}$F-FDG PET
  - $^{123}$I-MIBG
**111**Indium-DTPA-Octreotide

**111**In-octreotide is a conjugate of 8 of the amino acids from somatostatin (inhibitory peptide). Labeled with Indium-111.

Highest affinity for subtype 2, overexpressed in NET.

Intensely somatostatin receptor avid lesion
**$^{111}$Indium Octreotide**

- Sensitivity of 80-90% to detect carcinoid tumors; 50-70% for pancreatic NET; specificity 88-97% for both
  - Wong et al. *Clinical Radiology* 2012 EPUB

- Functional pancreatic NET (not insulinoma): sensitivity 90%, specificity 80%
  - Insulinomas drop to 50% sensitivity

- Octreotide (therapy) should only be given if insulinoma $^{111}$Indium Octreotide positive since could worsen hypoglycemia
  - Ricke et al. *Eur J Radiol* 2001;37:8
\[\text{\textsuperscript{111}Indium Octreotide: Debate on Utility}\]

- **Shaverdian et al. Ann Surg Onc 2012 [EPUB]**
  - Retrospective chart review 2001-2008
  - Not useful compared to CT/MR
  - But 8/74 patients new foci on SRS only
    - change management in 3/74

- **Nikou et al. Hepatogastroenterology 2005;52:731**
- **Usmani et al. Med Princ Pract 2011;20:356**
  - Performed better than CI and multiple new sites found
  - Changed surgical strategy in 32%
Patient Preparation for $^{111}$Indium Octreotide

- Stop octreotide treatment for 3 days
  - on depot wait just before next injection
- No other preparation
- In cases of insulinoma give 5% dextrose while injecting $^{111}$In octreotide
- Imaging 4 hours post injection and sometimes 24 hours
The Tools You Have

- Important that imaging is of the highest quality
- SPECT-CT is mandatory
    - SPECT only, fused to separately acquired CT or MR acceptable
- Limitations include size of lesion, cystic, and/or low expression somatostatin receptors
- False positive from nearby physiologic uptake (SPECT-CT overcomes) and uncommonly infection/inflammation/other tumors
Intriguing Concepts

  - Compared 2 cohorts of well differentiated NET
  - Lack of $^{111}$Indium Octreotide uptake (and sst2) poor prognostic factors even in absence of therapy
    - also age and lack of clinical syndrome
  - Clinical syndrome 54% in SRS+; 33% in SRS- (p<.05)
  - Chromogranin A elevated 61% SRS+; 75% SRS- (ns)

- Suggests heterogeneity even with well-differentiated
- More studies like this needed
SPECT-CT at Emory University Hospital
Be aware

• Looking at different processes: MR and CT will find smaller and necrotic lesions in liver but may be nonspecific such as we saw with FNH.
  – also nodal enhancement nonspecific.

• $^{111}$Indium Octreotide looking at receptor density.
  – may see small lesions if receptor density high.
  – if not, even large lesions may not take up radiotracer.
Another patient…

- 62-year-old male diarrhea and flushing with known hepatic metastatic carcinoid without identification of primary lesion.
- Underwent right hemihepatectomy and multiple intraoperative RF ablations.
- Now symptom free.
- Post operative MR showed persistent hepatic lesions but no other foci.
$^{111}$Indium Octreotide showed the more active liver lesions but also 2 foci in RLQ
Retrospectively fused to MR: identified retroperitoneal node and primary ilial lesion

Changed Management
FDG is a glucose analog labeled with $^{18}$F: a positron emitting radionuclide (half life: 110 minutes)

- Malignant cells use more glucose than benign cells for energy
  - overexpress Glut 1-7 transporters
- FDG is nonspecific
- Normal cells utilize glucose too
Role of FDG PET in NET?

• Well differentiated NETs poor FDG uptake depending on degree of tumor differentiation and biologic behavior

• But there is a role in poorly differentiated tumors with more aggressive biologic behavior

• When other imaging including $^{111}$Indium Octreotide fail to localize may try FDG-PET

» Wong et al. Clinical Radiology 2012 EPUB
Role of FDG PET in NET?

- *Binderup et al. J Nucl Med 2010;51:704*

  - 96 patients with NET
    - All got $^{111}$Indium Octreotide, $^{123}$I-MIBG, $^{18}$F-FDG
    - Sensitivity 89%, 52%, 58% respectively
    - But $^{18}$F-FDG 92% sensitivity for Ki-67>15%
    - At one year followup 14 patients died of disease
      - 13/57 FDG PET positive patients died
      - 1/41 PET negative patients died
    - PET SUV also independent predictive factor for progression free survival
More Intriguing Concepts

  – 38 patients metastatic NET
    • SRS, CT, FDG PET
  – Most with FDG + early progressive disease
  – Most with SRS – early progressive disease
  – PET correlated with PFS and OS even with “low grade tumors”
  – On multivariate analysis to detect rapidly progressive disease, PET highest accuracy (92%) compared with SRS, WHO, Ki67, P53
Let’s look at one last patient…

- 77 year old female with metastatic NET
  - progressive liver predominant disease

- Symptoms controlled on Octreotide
  - Outside planar $^{111}$Indium Octreotide positive
  - $^{90}$Y microspheres therapy performed by IR and NM
Liver and Tumor Volumes from the \textsuperscript{111}Indium Octreotide SPECT-CT on Advanced Workstation
Hepatic disease stabilized but a year later breakthrough pain. Is the tumor now dedifferentiating?

Lack of uptake on $^{18}$F-FDG PET suggests it is not...
Return to Functional Neuroendocrine Imaging

- **$^{111}$Indium Octreotide** significant liver and extrahepatic disease so tumor still fairly well differentiated but now **not liver predominant**

- We will do a related diagnostic scan:
  - **$^{123}$I MIBG**
    - Metaiodobenzylguanidine
    - Norepinephrine analog. Imaged at 24 hours

- If there is uptake in metastasis can then offer therapy with the beta emitter $^{131}$I MIBG
Meta-iodobenzylguanidine (MIBG)

- More useful with pheochromocytomas than GEP NET but can evaluate for $^{131}$I-MIBG therapy
    - $^{111}$Indium Octreotide better with most GEP NET but MIBG about equal with functional
- Preparation more involved with many more medications that must be withheld
  - Tricyclic antidepressants, nasal decongestants, catecholamine agonists, calcium channel blockers
- Block thyroid with Lugol’s solution
$^{123}$I MIBG

Uptake in liver but also mesenteric and retroperitoneal nodes and other distant disease
$^{131}\text{I} \text{ MIBG Therapy}$

- We saw her in consult
  - Candidate for high dose $^{131}\text{I} \text{ MIBG}$ therapy

- Not a cure but multiple studies show efficacy
    - >50% improved symptoms with increased survival
  - Postema et al. Cancer Biotherapy & Radiopharm 2009;24:519
    - Symptomatic relief in the vast majority of patients treated
    - Biochemical responses in about half
    - Radiographic responses in roughly one third
Other Radiopharmaceuticals

- $^{68}$Ga-DOTA-somatostatin PET analogues
  - Sensitivity 82-100%; specificity 92-100%
  - DOTANOC, DOTATOC, DOTATATE
  - Available in Europe
  - Ga-68 generator
    - Half-life: $^{68}$Ga = 68 minutes
  - Many advantages including better imaging of PET versus SPECT; 2 hour imaging vs 4-24 hours.

- $^{18}$F DOPA PET
  - Most sensitive for functional carcinoid, lower sensitivity for other NETs
Therapy

• In USA: only I-131 MIBG is approved as off-label use
• High dose $^{111}$In Octreotide under IND only
• Tyr-3-Octreotide coupled with yttrium-90 (Beta emitter)
• Also $^{177}$Lu analogues under study
Summary

• Always start with multiphasic MR or CT depending on local capabilities

• $^{111}$Indium Octreotide
  – Reasonable (optional) baseline study for whole body screening, confirm management, and/or determine if tumor is tracer avid for future utility
    • depends on your patient population and practice
    • quality of all imaging modalities
Summary

• $^{111}$Indium Octreotide helpful:
  – Conventional imaging equivocal or less than diagnostic
  – Imaging findings do not fit clinical impression
  – NET of unknown origin
  – Direct biopsy to most active lesion
  – Rising tumor markers and negative conventional imaging
  – Unresectable/metastatic to assess disease burden and determine global uptake for potential Octreotide therapy
    – especially in patients without hormonal symptoms
Summary

- FDG PET for aggressive tumors if SSR imaging negative

- $^{123}$I-MIBG for inoperable progressive extrahepatic predominant disease to evaluate for $^{131}$I-MIBG
  - If liver predominant consider Y90 microsphere

- More research needed on best utility of molecular imaging for prognostic and management decisions
  - research probably best done with DOTA-PET